Chapter 7

# BEHAVIORAL AND NEUROPHYSIOLOGICAL CHANGES WITH EXPOSURE TO IONIZING RADIATION

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# INTRODUCTION

The use of nuclear weapons in military conflicts will significantly challenge the ability of the armed forces to function. The thermal and overpressure stresses of conventional weapons will be significantly intensified during a nuclear battle. In addition, military personnel will have to contend with the hazards of exposure to ionizing radiation, which will be the main producer of casualties for nuclear weapons of 50 kt or less. Present projections of nuclear combat operations suggest that between one-half and three-quarters of the infantry personnel targeted by a tactical nuclear weapon would receive an initial radiation dose of 1.5-30.0 Gy.[1] This acute dose of ionizing radiation could dramatically affect a soldier's ability to complete combat tasks successfully. This, in turn, may ultimately affect the outcome of the armed conflict.

Information about the consequences of ionizing radiation may be derived from the following: *(a)* the nuclear detonations over Hiroshima and Nagasaki, *(b)* clinical irradiations, *(c)* nuclear accidents, and *(d)* laboratory animal research. Each of these sources has certain constraints. The Hiroshima and Nagasaki data are of limited value since there was no scientific assessment of behavior, and the reports were anecdotal, often conflicting, and not easily tied to specific radiation doses. Clinical irradiations are also of questionable value because precise measures of behavior are not usually recorded, and patients are behaviorally compromised by their illnesses or the chemical therapy being used. Nuclear accidents have been few, and little behavioral information has been obtained from those that have occurred. Although information on human radiation exposure is normally preferred, the paucity of data forces us to rely on animal research.

However, animal research brings with it problems of extrapolation. While the relevance of animal models to human behavior has been frequently shown in the study of toxic effects of ionizing radiation,[2,3] different species (even strains within species) may have different responses or sensitivities to radiation exposure.[4] It is important to understand the specific radiosensitivity of the animal model so that the radiation dose required to produce a similar effect in humans can be reasonably estimated. For example, in humans the lethal dose for 50% of cases after 30 days ($LD_{50/30}$) is 4.5 Gy, whereas in monkeys the $LD_{50/30}$ is 6.0 Gy. Similarly, the monkey is more radiosensitive than the rat ($LD_{50/30}$ = 7.5 Gy) or the mouse ($LD_{50/30}$ = 9.0 Gy).[5,6] Clearly, these classic $LD_{50/30}$ values are estimates, because they will vary with the animal strain, housing conditions, and other factors. However, the values do give a sense of the relative radiosensitivity of the animal models most often used in radiation research, and will help to put into context the radiation doses cited in this chapter.

Variations in radiosensitivity must also be considered when measuring animal behavior. For instance, at specific doses or dose rates, most animal models show a rapid, transient decrease in performance; however, this is not true for some dog or mouse strains.[7-9] Differences in CNS sensitivity to radiation have also been shown. The primate brain may be more sensitive to radiation damage than the rat brain.[10] Although differing sensitivities of animal strains can be enigmatic, they can be meaningful research tools that reveal physiological substrates of natural radioresistance.[9]

## BEHAVIORAL CHANGES IN IRRADIATED ANIMALS

Radiation has significant effects on a variety of behavioral factors, including *learning, performance,* and *naturalistic and social behaviors.* However, this list is not a complete taxonomy of behavior. For example, performance can be somewhat arbitrarily separated into tasks having a strong cognitive component and tasks having a strong motor component. Also, an important distinction can sometimes be made between learning and performance. In its simplest form, learning is reflected by a linkage of a stimulus and a response. However, performance also depends on the organism's capacity to make a response. Thus, postirradiation changes in behavior may reflect deficits in either performance or learning (or both). Psychologists consider these concepts to be distinct, but in some cases it is difficult to separate them, especially in animal studies. Whether the mechanism of radiogenic behavioral change is based on deficits in learning, attention, retrieval, capacity to perform, or group disturbance, any of these disruptions can potentially determine an organism's ability to function in a nuclear environment.

### Learning and Memory

Pavlovian conditioning paradigms are especially useful in distinguishing between learning and performance in animals. Studies suggest that learning can be altered by exposure to ionizing radiation. For example, rabbits were conditioned to associate a light-and-tone stimulus with the respiratory reflex of apnea that is produced by the inhalation of ammonia vapor.[11] Exposure to 15 Gy of cobalt-60 gamma radiation resulted in the absence or considerable reduction of conditioned apnea. In contrast, the unconditioned apnea (normal response to ammonia inhalation) was enhanced after irradiation, suggesting that the animal’s performance capacity was still intact. These classical conditioning data suggest that (at least under the stated circumstances) radiation exposure can alter memory, and that this function is separate from the animal's performance.

Experiments using operant techniques may also be designed to allow some distinction between learning and performance. If a task can be selected in which a learning deficit is represented in a more rapid or vigorous response, then it may be possible to rule out lethargy or reduced physical capacity as the primary mediator of a behavioral change. For example, rats were trained to stay in a lighted area in order to avoid footshock in the adjacent dark area, which they normally preferred.[12] The latency of the subject's movement from the safe, lighted area to the electrified dark side was an indicator of learning. Thus, a rapid move into the hazardous chamber suggested that the subject had a learning deficit. This kind of learning appears to be extremely sensitive to disruption by radiation exposure, since an electron dose of only 0.001-0.1 Gy can produce significant *retrograde amnesia.* Retrograde amnesia is a short-term memory loss, or an inability to recall recent events, following trauma or a novel event. In this case, the forgotten event (footshock) occurred only seconds before the novel event (irradiation). The amnesia lasted for 4 seconds, was dependent on dose rate, and was produced by either electron or X irradiation.[13] The mechanism of radiogenic amnesia is still in question. However, sensory disruption, primarily of the visual system, may explain the memory loss.[12,14,15] These data support the idea that radiation affects some component of learning or memory, and the data agree with others suggesting that radiogenic disruptions in behavior may not merely reflect non-associative factors.[16]

Human memory may also be impaired by radiation exposure. For instance, a few cases of acute retrograde amnesia were reported by persons who survived the bombing of Hiroshima.[17] Five years after the attack, deficits in memory and intellectual capacity were noted in persons experiencing radiation sickness.[18] These data seem consistent with the Soviet studies reporting memory deficits in patients who had undergone therapeutic irradiations.[19] However, although the human data corroborate the animal studies, they suggest that memory impairments may have been strongly influenced by the other stressors of war or illness.

Improved or unaltered learning capacity or performance after exposure to radiation has been reported. For instance, although radiation caused a dose-dependent decrease in monkey activity and appetite, animals showed no loss of ability to solve “even the most complex learning problems” at doses of 2-10 Gy of X radiation.[20] Task performance was actually enhanced in some studies after 6.5 or 10 Gy of X rays.[21] This enhancement may have been due to decreased general activity and lowered distractibility.[22-25] In fact, performance and learning may have been better in the irradiated animals because the radiation exposure acted as a mild sedative, thus reducing anxiety and distractions.[26] After exposure to several types of radiation, some animals showed superior learning when a premium was placed on paying attention to the site of a food reward, although their performance was worse on tasks requiring attention to peripheral stimuli.[23] In a series of difficult discrimination-learning problems, the performance of monkeys exposed to 3.5 Gy of mixed neutron-gamma radiation was superior to that of control monkeys.[22] Finally, another series of studies with monkeys indicated that radiation does not disrupt performance on memory tasks.[27]

Rodent studies yielded similar findings. For example, adult rats given 2-3 Gy of whole-body radiation did not differ from control animals in learning or remembering a water maze.[28] The rat's ability to maintain a temporal discrimination was not altered following 3 Gy of X rays.[29] Other maze-learning studies were done with rats using either food or water rewards or escapes from aversive water or shock.[30] In these experiments, either no change in the rate of acquisition or improved acquisition (faster running times and improved retention) was found in rats exposed to 1-30 Gy of radiation.[24,28,31,32] Similarly, mice exposed to 8-72 Gy showed no reduction in their ability to acquire an avoidance response.[33,34] When mice were conditioned to shuttle back and forth between adjacent chambers while being exposed to 0.001 Gy/hour (total dose of 10 Gy),[35] no differences were found.

Although some of the behavioral radiobiology literature suggests that learning and performance are rather radioresistant, most studies have reported postirradiation deficits. For instance, maze-learning behavior was reduced after X-ray exposure up to 10 Gy.[36] After it was suggested that more challenging tasks would be more radiosensitive than easy ones, rats were found to have a temporary reduction in their ability to reorganize previously learned material after exposure to 4 Gy of gamma radiation.[37]

## Cognitive Performance Tasks

The behavioral tasks in this category generally require discrete physical movements and functional cognitive processes, such as timing, decision making, or concept formation. The tasks that require learning in the laboratory are usually difficult to teach to the animals, and significant time is required to establish stable performance before testing for radiation effects.

Generally, radiation-induced cognitive effects have been reported in primates only after intermediate or high levels of radiation, and often these decrements were still found if the animals were tested months or years later. For instance, a deficit in delayed response was noted in monkeys for a few days after an 80-Gy irradiation.[38] Cynomolgous monkeys tested 2.0-3.5 months after a 20-Gy head-only exposure to X or gamma rays showed a deficit on a discrimination problem series.[39] Their response was similar to that of chimpanzees tested 2-5 years after exposure to 4 Gy of whole-body gamma radiation. In this case, the chimpanzees performed an oddity-discrimination task in which an odd object was selected from a group of similar objects. In other models, delayed (2-week) deficits in performance accuracy occurred in dogs after 3 Gy of X rays,[40] while deficits were found in rats only after prolonged cumulative exposure.[41] Thus, some cognitive deficits occurred only following high radiation exposures, and the deficits were delayed or chronic.[42]

A recent lever-pressing study examined dose-effect relationships, time-course effects, reversibility of behavioral decrements, and behavioral specificity.[43] In this experiment, rats were maintained under restricted feeding conditions and trained to press a lever under either a fixed-ration (FR) 50 schedule or a fixed-interval 2-minute schedule of milk reinforcement. In the fixed-ratio task, animals made 50 lever presses for one reward; in the fixed-interval task, the first lever press after 2 minutes was rewarded. Acute doses of 0.5-9.0 Gy of gamma radiation were given at a dose rate of 2.5 Gy/minute. These studies indicated scheduled-controlled performance changes that were dose-dependent, reversible, and behavior-dependent (that is, ratio responses were more affected than interval responses). More important, even at marginally lethal levels using positive reinforcement, radiation disrupted the more physically demanding fixed-ratio performance. These findings suggest that tasks with cognitive components may be radiosensitive if the requirements are sufficiently complex or demanding.[37,44]

Experiments with monkeys have simulated pilot missions after a nuclear confrontation in order to assess crew and aircraft vulnerability and survivability. They involved moderate doses (11 Gy or less) of either neutron or gamma radiation delivered in dose rates simulating either combat (rapid doses) or fallout (protracted doses). The first of this series was a fallout study in which a dose of 3 Gy was delivered over 12 hours to monkeys performing a discrete response task, which required pressing a lever after a light came on. The task was performed for either food reward or shock avoidance.[45,46] A loss of efficiency occurred in two of eight negatively reinforced monkeys and in two of seven food-reinforced monkeys. Delayed reaction time was noted in three monkeys in each group. In addition, four food-reinforced monkeys and one avoidance monkey showed emesis.

In another pilot simulation study, monkeys were required to maintain their chairs in a horizontal position by compensating for pitch and roll to avoid shock.[47,48] Three Gy of gamma radiation were delivered over 72 hours at dose rates from 0.014 Gy/minute to 0.01 Gy/hour. Monkey performance was relatively unimpaired, but all subjects demonstrated classic prodromal symptoms, including productive emesis. Given the common finding that behavioral effects from low dose rates are usually less than those observed from high dose rates, it is not surprising that the pilot simulation study revealed lesser radiation effects than the discrete response task did.

Other flight-simulation research was conducted with monkeys trained to perform a multiple avoidance task and exposed to pulsed doses of 5.0-6.8 Gy of neutron-gamma radiation (5.5:1 ratio).[49] The task required monkeys to respond on an appropriate lever below three randomly illuminated lights. On the exposure day, five subjects exhibited decreased efficiency, seven had increased reaction time, and six experienced productive emesis within 3.5 hours after exposure. Follow-up measurements indicated that as postirradiation time increased, the performance of the subjects gradually decreased. Again, although the behavioral degradation was not severe, it was greater than in the low-dose, low-dose-rate studies. Further research used even higher doses, exposing monkeys to 11 Gy of neutron-gamma radiation.[45] On the exposure day, all eight subjects had significantly degraded response accuracy, seven had increased reaction time, and seven experienced productive emesis. While the onset of degradation produced by 11 Gy was not particularly rapid in the animals, either the emesis alone or similar direct behavioral effects in humans may be sufficient to prevent pilots from flying military missions.

### Motor Performance Tasks

Many motor tasks require not only extensive training but also physical conditioning in order to establish baselines of behavior. In general, these are tasks that require physical exertion associated with the movement of large striated muscles.

Several studies revealed chronic deterioration of motor performance after doses of radiation at or below the $LD_{50}$. For example, long-term (42-week) progressive deterioration of forced wheel-running behavior occurred in mice exposed to an $LD_{50}$, dose of neutron radiation.[50] There was a significant reduction in the motor capacity of rats that daily swam to exhaustion before and after exposure to 3-10 Gy of X rays.[4] In this study, reduced swim times occurred 2 weeks after exposure, with maximum performance deterioration by 4 weeks; the effects were dose related. However, when dogs exercised daily on a treadmill for 30 days after exposure to 1-3 Gy of X rays, long-term deterioration was not confirmed.[51] Performance deteriorated only as dogs neared death after exposure to 3.0 Gy of radiation. The literature on behavioral radiobiology contains frequent examples of experiments in which post-irradiation dog performance does not confirm the behavioral decrements seen in the rat, the monkey, or even the human; thus, the dog may not be a valid model for the study of these effects.

These early studies may be contrasted with more recent work identifying the transient changes in motor performance after supralethal doses of ionizing radiation. Significant deficits have been noted in a variety of animal species performing different physically demanding tasks. Miniature pigs that were required to shuttle between adjacent compartments in order to avoid shock experienced transient behavioral deficits after exposure to 15-150 Gy of gamma or mixed neutron-gamma radiation.[52-54] Transient behavioral incapacitations were reported in rats trained to move up to a safe shelf or stay on an accelerating rotating rod in order to avoid shock.[7,55-58] Rhesus monkeys showed a transient reduction in performance in a running wheel task after exposure to 13-49 Gy of mixed neutron-gamma ra-diation.[59]

Performance of a physically demanding task can alter survival after irradiation. A rat's swimming to exhaustion before and after irradiation will significantly reduce performance and lower the $LD_{50}$ by about 2 Gy.[60] The increased mortality was proportional to the number of exercise trials during the initial 3 weeks after radiation exposure[61] and also to the dose received.[4] Some recent data support this general finding. Rats performing a strenuous, shock-motivated motor task after irradiation had a lower $LD_{50}$ than animals not required to perform this task (Figure 7-1).[62] However, the finding of performance-stimulated mortality is not universal. No mortality changes were noted in dogs and mice that ran in a motorized activity wheel and a motorized treadmill, respectively.[63,64\]

The rat-swimming model also revealed a radioresistant benefit when the level of pre-irradiation physical activity was adjusted. Rats that swam to just short of exhaustion before irradiation showed increased radioresistance and a higher $LD_{50}$.[65] In a follow-up study, rats recovered from radiation effects sooner if they swam to just short of exhaustion before the radiation exposure.[66] A positive correlation has been found between the initial preirradiation level of spontaneous activity and survival after X irradiation.[67] It was speculated that the beneficial effects for rats of swimming to pre-exhaustion came from radioprotective anoxia. Apparently, animals that reach exhaustion before or after irradiation will show increased radiation effects, in contrast to rats who became more radioresistant if their preirradiation exercise was stopped before exhaustion. The timing and stress of the physical exercise may explain the differing results reported here.

Sensitive measures of the strength and endurance of monkeys reveal that the force of pulling is not reliably impaired after a 4-Gy radiation exposure.[68] Similarly, the postirradiation force of motor response in rats is quite stable for days after a dose of 4.5 or 9.0 Gy.[69] A significant reduction in these measures of strength is seen only when death is imminent.

## Naturalistic Behaviors

Naturalistic behaviors are a normal part of an animal's response repertoire, and their performance requires no laboratory training. Naturalistic behaviors often evaluated in the study of radiation effects are spontaneous locomotion, social interaction (such as sexual and aggressive behaviors), consumption behaviors (eating and drinking), taste aversions and emesis.

***Locomotion***. Spontaneous locomotion is a naturalistic behavior that is convenient to measure and provides a relatively powerful tool for studying performance. Activity is of interest because radiation is known to produce malaise, along with other prodromal symptoms of general weakness, fatigue, headache, nausea, anorexia, vomiting, hemorrhage, and drowsiness or insomnia.[70]

An acute whole-body dose of 2-7 Gy of X radiation produced immediate depression in the rat's volitional activity-wheel performance.[71] These data were confirm-ed by others using guinea pigs, hamsters, rats, and primates.[36,38,72,73] Locomotion was even depressed in rats that were deprived of food for 6 weeks after irradiation and tested daily.[74] (These data are significant because food deprivation normally increases activity.) This locomotor depression lasted a few days, and was followed by partial recovery.[71] At doses above 4 Gy, a second decrease in activity occurred after 1 week, suggesting that more than one response mechanism may be involved. This biphasic response[75] is similar to clinical symptoms in humans.[67]

In a recent study of the effects of sublethal doses of gamma rays on locomotion, mice were monitored for 30 days after exposure to 0.5-7.0 Gy of cobalt-60 radiation.[76] Locomotion after the 7-Gy exposure gradually dropped until it reached a significant low 15 days later. Recovery of locomotion occurred by day 19. Thus, alterations in locomotion were detected at less than the $LD_{50/30}$ (7.6 Gy).

***Curiosity and Investigative Behaviors***. Curiosity and investigation are other naturalistic behaviors that have been measured. Chimpanzees given 4 Gy of gamma radiation made fewer attempts to solve a variety of puzzles.[25] This deficit seemed to be independent of changes in capacity, because measures of dexterity and strength were unchanged in the same animals. After monkeys were exposed to 4 Gy of X rays, their manipulation of objects in the home cage and their rapid expenditure of energy decreased; sitting time lengthened; and chewing, scratching, grooming, and number of cage movements decreased.[68] A systematic study of home-cage behavior was made with pairs of monkeys after 4 Gy of whole- body exposure of both animals in each pair.[10] Ten-minute structured observations were made twice daily. To control for debilitation, the instances of each category of behavior were divided by the number of times that the identifiable behavior occurred in that time period. The irradiated animals showed reliable deficits in curiosity, more inner-cage-directed movements to well-known stimuli, and fewer instances of outer-directed movements or attention to things outside the cage. Similarly, reduced curiosity or reduced visual exploration (looking around) has been observed in rats after receiving 50 Gy of X rays.[72] Since some of the procedures with the monkeys tried to factor out general malaise, these findings suggest a specific change in curiosity and attention that developed after irradiation.[77]

***Social Behavior***. Because military units are social structures, the effect of radiation exposure on social behavior is a military concern. The most commonly studied social behaviors are aggression and fighting. Primate studies showed that aggression in monkeys[10,30,78,79] and the social interactions of chimpanzees[39] significantly decreased following irradiation. Fighting among male mice (a very common group home-cage activity) decreased with an increasing dose of X radiation, but all signs of fighting were not totally suppressed until shortly before death.[80] An intruder mouse introduced into the home cage of another mouse continued to be attacked for several days after the resident mouse had received 10 Gy of gamma radiation.[81] These behaviors persisted until the resident mouse showed radiogenic moribund behavior.

An extreme variant of aggression is muricide (mouse killing), which some rats exhibit spontaneously. Muricide was frequently suppressed after radiation exposure.[82] Footshock can be used to induce aggression, however, and 7 Gy of gamma radiation can stimulate this response.[83] The increase in this unnatural type of aggression may be related to radiation-induced increased irritability.[5] This hypothesis is consistent with the report that head-irradiated male rats were more "emotional" than were the sham-irradiated controls during the first 30 days after exposure.[72]

Changes in aggressiveness may reflect a more general social phenomenon. Several investigators reported that mortality following irradiation will increase if rats are kept in high-density housing.[30,84-86] Presumably, the combined stresses of maintaining territory and being exposed to radiation increased the rat's mortality from the radiation. The mechanism of this aggregate toxicity is being studied.[87] The effects of emotionality or dominance following irradiation have been studied, but neither factor seemed to alter postirradiation mortality.[85] Finally, frequent sexual activity during the 30 days after exposure was found to increase the mortality rate of male mice.[88]

***Consumption Behaviors***. Exposure to ionizing radiation is known to reduce food and water consumption and to produce nausea and vomiting.[30,67] Intake will be decreased, at least initially, depending on the radiation dose and dose rate.[29,72] Instances of radiation-induced anorexia and adipsia have been noted.[75,89] Subjects will not perform for food after 10 Gy of radiation, but will continue to work to avoid electric shock, suggesting that consumption behaviors are relatively radiosensitive.[90]

Changes in food preferences have also occurred after irradiation. Monkeys chose apples and carrots more frequently and peanuts less often after exposure to 4 Gy of whole-body X radiation.[91,92] The changed preferences lasted 4 weeks and were dose dependent. Because the mouth, throat, and stomach are highly sensitive to abrasion after irradiation, the newly preferred foods may have been easier for the monkeys to swallow.[10]

***Taste Aversions and Emesis***. Animals readily learn to associate gastrointestinal upset and malaise with a novel taste and smell, and will avoid the new substance when later exposed to it.[93] Results indicate that a *conditioned taste aversion* (CTA) can occur at doses as low as 0.25 Gy and can be reliably achieved at 0.5 Gy. Because this may be the most reliable and radiosensitive form of behavioral conditioning, CTA has been extensively used as a model of radiation-induced gastrointestinal distress and emesis.[94]

The relationship of emesis and performance decrement is complex. When gamma radiation is used, the $ED_{90}$ (effective dose for 90% of cases) for monkey emesis is 8 Gy.[95] Emesis is more likely to be produced after irradiation with neutrons than after gamma-ray exposure.[96] Up to 10 Gy, increasing doses of radiation in the monkey correspond with the enhanced likelihood of emesis.[97] However, above 10 Gy, the number of monkeys that vomit decreases with increasing dose. The reason for this high-dose inhibition of emesis is largely unknown, but it may be that doses above 10 Gy interfere with the transmission or reception of afferent vagal impulses from injured organs, which normally play a part in this response. The report that no emesis occurs during early behavioral incapacitations is fairly common. No relationship was found between emesis and early performance deficits in monkeys exposed to up to 50 Gy of mixed neutron-gamma radiation and performing in a physical-activity wheel.[59] Similar visual-discrimination performance results were seen in monkeys pulsed with 22 Gy of radiation.[44,98] Animals not incapacitated but receiving the same dose as incapacitated animals will vomit as expected.[94] Although the data are revealing, the relationship between radiation- induced emesis and behavioral deficits must be clarified.

Despite some ambiguity in the animal data, emesis will almost certainly interfere with the performance of some critical military tasks, such as those that require the wearing of artificial breathing devices.

## COMBINED INJURIES

Nuclear war will produce few "pure" radiation injuries. It is more likely that victims will experience burns, wounds, and perhaps trauma from chemical agents and environmental stresses combined with the damage from ionizing radiation. The physiological effects and treatment of these combined injuries have received significant attention.[99,100] Less clear are the behavioral consequences from combined traumas that include irradiation.

Mice were exposed to 3 Gy of neutron-gamma radiation and some of them were then exposed to the further trauma of a wound or burn.[101] The radiation exposure alone caused significantly depressed measures of locomotion. In addition, the wound injury increased the harmful effects of radiation, while the burn injury did not.

In a study of the combined effects of radiation (7 Gy) and an anticholinesterase agent (physostigmine, 0.1 mg/kg), rats were evaluated on a behavioral test battery that included measuring their balance on a rotating rod and recording several components of their locomotor activity.[102,103] At 45 minutes after irradiation, a radiation-only group had a 30% deficit in performance, while a physostigmine-only group had a 40% deficit. A combined-treatment group showed a 60% performance deficit on the rotating rod task. In fact, all measures of performance indicated that the effect of combined ionizing radiation and physostigmine was much greater than the effect of either insult alone. In a follow-up dose-response study, rats were required to balance on a rotating rod.[104] As in the above experiment, physostigmine and radiation each produced a dose-dependent behavioral decrement when presented alone. A synergistic behavioral effect was observed after combined treatment with the chemical and radiation.

Environmental and combat stresses may also combine with radiation injuries to increase behavioral decrements. For example, a study in monkeys to test for synergy between radiation and motion effects reported an emesis $ED_{50}$ of 4.5 Gy for radiation alone and 2.6 Gy for radiation plus motion.[78] Radiation may reduce the tolerance of animals to the stress of G forces (acceleration) as measured by lethality and pathomorphological and cardiovascular end points.[105-107] But other experiments report that an animal's resistance to critical acceleration increases for several days after irradiation (7-8.5 Gy).[107,108] The variables of timing and direction of acceleration combine with radiation dose factors to complicate the issue. However, to the best of our knowledge, only one behavioral experiment has studied the combined effects of radiation and G forces. Rats were exposed to 9.5 Gy of X rays over a 24-hour period, followed 5-7 days later by 4 minutes of positive 10 G of acceleration stress.[109] Compared to animals that were only irradiated, the authors reported that rats that received both stresses exhibited a significant (about 25%) but transient decrease in the ability to learn new mazes. However, no change in the number of errors in an already-learned maze was observed in rats after combined treatment with positive G forces and radiation.

Other environmental stresses can alter the effectiveness of radiation on behavior or lethality. For instance, daily exhaustive exercise, continuous exposure to cold (6°C), or continuous exposure to high altitude (15,000 feet) considerably reduced the time to death and the incidence of death after irradiation.[30] Taken together, these data suggest that the behavioral effects of radiation may summate or act synergistically with other stresses. Therefore, any estimates of battlefield performance decrements that do not include these factors will probably be lower in number and degree than the behavioral decrements actually observed in a military conflict.

## EARLY TRANSIENT INCAPACITATION AND OTHER EARLY PERFORMANCE DEFICITS

For the military, an abrupt inability to perform—aptly termed early transient incapacitation (ETI)—is a potentially devastating behavioral consequence of radiation exposure.[110] An idealized individual ETI profile is shown in Figure 7-2. Prior to irradiation, performance is at maximum efficiency. But 5-10 minutes after exposure to a large, rapidly delivered dose of ionizing radiation, performance falls rapidly to near zero, followed by partial or total recovery 10-15 minutes later. Delayed ETIs may also occur at about 45 minutes and 4 hours after irradiation. In various animal models, ETI is a strikingly short, intense phenomenon. A less severe variant of ETI is *early performance decrement* (EPD), in which performance is significantly degraded rather than totally suppressed (Figure 7-2). Until recently, it was presumed that ETI and EPD would occur only at supralethal radiation doses and that, after behavioral recovery, death would occur in hours or days. However, more recent data reveal that high doses may not be necessary to produce these effects.[44,111]

Transient EPDs occur in monkeys, rats, and pigs performing a variety of tasks, and the deficits are believed to occur in humans. However, this finding is not universal in animals, since EPD does not occur in some strains of mice[9,112] and dogs.[8,113,114]

## Task Complexity

When ETI was first observed in monkeys in the early 1950s, the dose levels reported to produce it were quite high, perhaps because the behaviors tested were relatively undemanding and were therefore radioresistant to disruption (Table 7-1).[110,115,116] These early measurements involved either the simple observation of untrained monkeys or their performance of a relatively easy continuous-avoidance task (pressing a lever to avoid shock when a light came on in the operant chamber). In the context of these minimal requirements, the effective ETI-producing radiation doses were found to be 50 Gy or more. When a more complex shock-avoidance visual-discrimination task was later used, the median effective dose to produce ETI was reduced to approximately 22 Gy (Table 7-1).[117,118] On this visual-discrimination task, monkeys were required to discriminate (within 5 seconds) between a circle and a square (the square was always the correct choice) randomly presented on backlit press-plates every 10 seconds. Monkeys were trained later on a variant of this visual-discrimination task, in which the temporal response criterion (set at 0.7 seconds) approached the reaction time of the animal.[44] Under these conditions (speed-stress visual discrimination), the median effective dose to produce ETI was approximately 9 Gy (Figure 7-3). Thus, the dose of radiation required to disrupt behavior is directly related to the complexity of the task that the animal is required to perform; that is, complex or demanding tasks are more radiosensitive than easy tasks.

Another reason that the radiation dose required to disrupt performance was presumed to be high is that ETI is an all-or-none, relatively insensitive end point. When the ETI data are analyzed with a more sensitive behavioral end point (that which measures a significant change from a baseline response rather than only a total cessation of response), the disruptive dose is even lower (Table 7-2), approaching the $LD_{50}$ for the monkey.[44] Furthermore, the $ED_{50}$ for transient behavioral deficits in monkeys may be as low as 3 Gy if the animals are performing a more difficult task requiring both visual discrimination and memory.[111] If these data can be generalized to the human, they suggest that under certain circumstances, relatively low doses of radiation may cause rapid, transient disruptions in performance.

The issues of task demands and task complexity influencing the effective radiation level are common in the investigation of ETI. For instance, the dose of radiation required to disrupt performance was compared for three tasks: the visual-discrimination task (described above, with a 5-second response time), a physical activity task, and an equilibrium-maintenance task. In the physical activity task, monkeys ran at 1-5 mph in a nonmotorized, circular cage.[59] In the equilibrium task, monkeys maintained horizontal alignment by compensating for the pitch and roll of a platform on which they were seated.[119] Performance on all three tasks was assessed in monkeys exposed to a 25-Gy pulse of neutron-gamma radiation. Visual-discrimination performance with a 5-second response time was disrupted the least, with performance returning to about 80% of baseline by 20 minutes after irradiation (Figure 7-4). Wheel-running performance was disrupted the most, and performance returned to only about 50% of baseline at 60 minutes after irradiation. The above data suggest a hierarchy of behavioral effectiveness, with obvious implications for military missions.[44,86]

**Radiation Dose**

A variety of radiation parameters, including dose, can significantly influence EPD. Low doses of radiation can sometimes produce behavioral changes, such as locomotor activation,[120] that are in contrast to the locomotor depression observed after high doses.[121] Beyond a certain threshold, more radiation tends to produce increasingly depressed measures of performance.[7,44,59] For example, in a recent study, 7.2 Gy was the $ED_{50}$ for the speed-stress visual-discrimination task.[44] However, all monkeys exposed to 14.1 Gy of mixed neutron-gamma radiation showed transient EPD, while only one of five subjects showed this deficit at 6.8 Gy. Thus, at 7.3 Gy (Figure 7-3), the incidence of performance suppression ranged from 10% to 90%. These radiation dose-response curves for measures of behavior in some ways parallel the curves observed for a number of end points, such as emesis and lethality.[122]

**Radiation Dose Rate**

Another radiation factor that can influence behavior is exposure dose rate. Monkeys trained to perform a delayed matching-to-sample task, involving visual discrimination and short-term memory, were exposed to 10 Gy of gamma radiation at dose rates of 0.3-1.8 Gy/minute (Figure 7-5).[111] Only 7% of the subjects demonstrated transient EPD after a dose rate of 0.3 Gy/minute, while 81% showed behavioral decrement after 1.8 Gy/minute. This increase of 1.5 Gy/minute raised the incidence of early EPDs by 73%.

Fractionated (or split) doses have less impact on behavior. For instance, monkeys performing a visual-discrimination task were exposed to a total dose of 50 Gy of gamma-neutron radiation delivered in a reactor pulse.[123,124] One group of monkeys received the radiation treatment in one 50-Gy dose; the other groups received 25 Gy at two intervals separated by zero time and intervals of 20, 30, and 40 minutes and 1, 3, 4.5, and 6 hours (Figure 7-6). Performance was more severely disrupted for subjects who received the whole dose at once than for subjects in the split-dose conditions. In a recent study with rats, a single acute exposure to 7.5 Gy of gamma radiation disrupted performance by reducing the rate of lever-pressing under an FR 20 schedule (thus, 20 lever presses would be required to terminate electric footshock).[125] Behavioral disruption was characterized by decreased response rates over the 40-day period after exposure.

However, when a different group of rats received a total dose of 7.5 Gy delivered at 1.5 Gy/day over 5 days, disruption in FR performance was significantly less.[125] Although other behavioral dose-rate effects have been reported,[126-131] this finding is not universal and may depend on the behavior being measured.[89]

## Radiation Quality

In addition to dose and dose rate, the type of radiation can influence early behavior deficits. It is generally accepted that high-LET radiations (such as neutrons) are more effective in eliciting biological responses and death than are low- LET radiations (such as gamma rays).[5] However, research has shown that the opposite is true when the end point is performance.[7,57,132] Neutron radiation was only 23% as effective as gamma radiation (based on $ED_{50}$) in producing ETI in pigs performing a shuttlebox task, which required the subjects to move back and forth between adjacent chambers in order to avoid shock.[52] In another study, the neutron-gamma RBE for monkeys performing a visual-discrimination task was 0.68; that is, gamma radiation was more effective than neutrons.[114] Also, in a comparison of neutron and bremsstrahlung (gamma-like) fields, it was reported that bremsstrahlung radiation was more effective in producing ETI than was neutron radiation.[117]

A recent comprehensive study of the behavioral effects of various radiation qualities was done with rats performing on an accelerating rotating rod. This shock-motivated task required each subject to maintain its position on a 2-inch-diameter gradually accelerating rod for as long as possible.[132] In this study, bremsstrahlung, electron, gamma, and neutron radiations were investigated, and a dose-response relationship was found for all radiations (Figure 7-7). A major finding of this research was that electron radiation was the most effective in producing EPD, and neutron radiation was the least effective. Gamma radiation was slightly more effective than neutrons. This is not the first time that electron radiation was found to be the most disruptive to behavior.[128] Thus, substantial support is accumulating to suggest that radiations of different qualities are not equally effective in altering animal behavior. Furthermore, since electrons are more behaviorally effective than high-LET radiation, the quality factors derived from these data may be different from those already established for damage to biological systems.[30]

Other factors that may affect behavioral disruption after irradiation include (but are not limited to) the physical well-being of the subject (sick or healthy, tired or rested), the presence or absence of physical shielding or pharmacological radio-protectants, and the exposure or nonexposure of the subject to radiation alone or to radiation and other stresses of the nuclear battlefield (such as blast, heat, or flash).

# THE NEUROPHYSIOLOGICAL BASIS OF PERFORMANCE DECREMENTS

## Sensory and Perceptual Changes

From the psychologist's viewpoint, sensory and perceptual processes are distinct, yet interrelated. The sensory process involves stimuli that impinge on the senses, such as vision, audition, olfaction, gustation, and skin sensation.[133] The perceptual process involves the translation of these stimuli by the CNS into appropriate overt or covert interpretation and/or action. Ionizing radiation can be sensed and perceived, and radiation-induced sensory activation can in fact occur at extremely low levels.[13] For instance, the olfactory response threshold to radiation is less than 10 mrad, and the visual system is sensitive to radiation levels below 0.5 mrad. Ionizing radiation is as efficient as light in producing retinal activity, as assessed by the electroretinogram. The visibility of ionizing radiation was reported shortly after the discovery of X rays and is now firmly established.[30]

***Vision.*** Although the visual system can detect a low radiation dose, large doses are required to produce pathological changes in the retina. This is especially true of the rods, which are involved in black and white vision.[67] Necrosis of rods has been reported after doses of 150-200 Gy in rats and rabbits, and after 600 Gy in monkeys. Cone (color vision) ganglion cells are even more resistant. At these high radiation doses, cataracts occur.[70] Monkey binocular thresholds did not change during the 100 days after 35 Gy of X radiation.[134] However, performance deteriorated rapidly after this period, so that by day 210, the animals were blind and no cortical photo-evoked responses could be obtained. Similar findings were reported in monkeys,[135] in rabbits,[136] and in human patients.[137]

Pathological changes in the visual system occur only at high doses, but this is not true of visual function. Rats trained to a brightness-discrimination task were not able to differentiate between shades of gray after 3.6 Gy or to make sensitivity changes after 6 Gy of whole-body X rays.[30] In mice, low-rate whole-body irradiation adversely affected brightness discrimination tested 3-5 months after exposure. Humans experienced temporary decrements in scotopic visual sensitivity 1 day after being exposed to 0.3-1.0 Gy of X radiation.[138] Long-term (20-36 days) changes in dark adaptation were reported in patients exposed to 4-62 Gy of X rays.[139]

In terms of visual acuity, only long-term deficits were reported in monkeys at 1-3 years after exposure to 3-60 Gy of radiation.[30,38] However, components of attention may have caused some of this effect. Since these exposures were not restricted to the visual pathways, brain damage (affecting the cognitive aspects of learning and/or the motor component of visual-acuity tasks) probably also existed. These data are consistent with observations of irradiated chimpanzees that showed impaired visual acuity and accuracy on visual-discrimination tests.[39]

***Audition and Vestibular Function***. Few adverse auditory changes have been noted after radiation exposure. Two Gy of X radiation to the head produced no changes in cochlear microphonics in rats examined up to 90 days after exposure.[140] Likewise, 5 Gy delivered to the rear half of a rat's brain did not affect intensity or frequency thresholds. However, a transient 5.5-decibel reduction in tone intensity threshold that lasted *2-5* weeks did occur in dogs after as little as 0.39 Gy of X rays.[29] At larger doses of 10-70 Gy, cochlear microphonics decreased in guinea pigs.[136]

The physiological substrate of hearing deficits has also been explored. Changes in the mouse ear following 20-30 Gy of whole-body X rays included cellular necrosis in the organ of Corti and in the epithelial cells of the ear canals.[30] Rats exposed to a whole-body dose of 1-30 Gy of gamma or X radiation demonstrated damage in the cochlea but not in the cristae of the vestibular inner ear or the middle ear. Human patients who received 40-50 Gy of therapeutic gamma radiation developed inflammation of the middle ear but only a temporary loss of auditory sensitivity and temporary tinnitus.[141] After being exposed to 20-80 Gy of X radiation, the hearing organs of guinea pigs were generally resistant to radiation.[142]

Vestibular function may be more radiosensitive than audition. Depressed vestibular function was reported in dogs after exposure to 3.5-5.0 Gy of proton radiation or 2 Gy of gamma radiation.[143] In another study, 5 Gy of gamma radiation depressed the electromyogram of vestibulartonic reflexes of rear extremity muscles in the guinea pig.[144] At higher doses of 4-22 Gy, loss of the pinna reflex (ear twitch) was noted in the mouse, and disturbances in equilibrium and other vestibular functions were noted in the burro and hamster.[131] Thus, depression in vestibular function may exist at doses close to the $LD_{50}$, and symptoms of vestibular disruption may last longer at higher than at lower doses.

***Other Senses***. Although the literature is sparse, olfactory and gustatory changes have been reported in patients exposed to therapeutic radiation.[145] Altered taste perceptions were also found in patients exposed to 36 Gy of X rays, with a metallic taste being the most common report. Transient changes in taste and olfactory sensitivity were also reported in radiotherapy patients and in the rat.[30]

The effects of radiation on the skin senses have also not been fully assessed. In the work that does exist, it is difficult to separate the direct receptor changes from the secondary changes arising from effects on the vascular system.[70] However, radiation-induced changes in pain perception have been addressed empirically. Gamma photons produced a dose-dependent analgesia in mice,[146] but data suggest that X or gamma rays did not alter the analgesic effects of morphine or the anesthetic effects of halothane in rats except under certain conditions.[147, 148]

In summary, whole-body radiation doses below the $LD_{50}$ do not appear to produce permanent sensory changes; however, transient alterations were reported at doses of 1-5 Gy. High levels of radiation can cause longer-lasting sensory impairments. Furthermore, high radiation doses that affect CNS morphology will also impair perceptual function.

**Radiation-Induced Changes in the Nervous System**

Although it is true that other organ systems may contribute to radiogenic lethargy and reduced responsiveness, the nervous system's central role in behavior makes it the presumed primary mediator of radiation-induced performance deficits. This presumption is supported by the fact that electrical or chemical stimulation of the brain can overcome some radiation-induced behavioral deficits.[121,149] In addition, experiments with partial-body shielding revealed the effectiveness of head-only irradiations in producing behavioral changes.[30] In this regard, severe long-term changes on a conditioned avoidance task (jumping a low barrier) and color visual-discrimination learning were reported in monkeys whose heads were irradiated with 20 Gy.[39] These data suggested functional derangement in the posterior association areas. Also, monkeys whose heads received X radiation (frontal and posterior association areas) 2 years earlier showed retarded learning on a problem-solving task.[38] Studies with rats, in which 50 Gy was delivered directly to the frontal cerebrum[16] or 25 Gy to the whole cerebrum, revealed a decreased ability to learn an alteration running pattern motivated by delayed reward.[150] Decreased learning was observed in rats whose heads were exposed to up to 8 Gy of X radiation and who then were required to learn a 14-unit maze.[151] Although the importance of the brain in radiation-induced behavioral change is well established, the question still remains: What specific changes in the CNS mediate the performance deficits observed after exposure to ionizing radiation? The answer is complex.

One hypothesis is that a sufficiently large radiation dose causes permanent brain lesions, demyelination, and necrosis, which in turn produce chronic behavioral deficits. In addition, short-lived behavioral phenomena may be mediated by transient vascular changes that induce edema or ischemia in the CNS. A second hypothesis is that performance changes are mediated by significant alterations in brain function due to changes in neurochemistry and neurophysiology. As is often the case, there is some truth in both hypotheses.

**Radiogenic Pathology of the Nervous System**

Radiogenic damage to brain morphology may occur after an exposure of less than 15 Gy and is a well-accepted finding at higher doses. However, these two conclusions have not always been reported. A review of many standard radiobiology textbooks reveals the common belief that the adult nervous system is relatively resistant to damage from ionizing radiation exposure.[152] This conclusion has been derived, in part, from early clinical reports suggesting that radiation exposures, given to produce some degree of tumor control, produced no immediate morphological effects on the nervous system.[153] However, this view was eroded when it was later shown that the latency period for the appearance of radiation damage in the nervous system is simply longer than it is in other organ systems.[154] Subsequent interest in the pathogenesis of delayed radiation necrosis in clinical medicine has produced a significant body of literature. Recent studies of radiation-induced brain damage in human patients have used the technology of computed axial tomography (CAT) to confirm CNS abnormalities that are not associated with the tumor under treatment but occur because of the radiotherapy.[155]

General (although not universal) agreement exists that there is a threshold dose below which no late radiation-induced morphological sequelae in the CNS occur. In laboratory animals, single doses of radiation up to 10 Gy produced no late morphological changes in the brain or spinal cord.[156,157] Necrotic lesions were seen in the forebrain white matter from doses of 15 Gy but not 10 Gy.[158,159] In humans, the "safe" dose has been a topic of considerable debate. Depending on the radiation field size, the threshold for CNS damage was estimated to be 30-40 Gy if the radiation is given in fractions,[160] although spinal cord damage may occur with fractionated doses as low as 25 Gy.[161] The difference between a safe and a pathogenic radiation dose to the brain may be as small as 4.3 Gy.[162]

It is clear that the technique used to assess neuropathology can profoundly influence its detection. In a recent preliminary inspection of neutron-irradiated brain tissue stained with silver to detect degenerating neural elements, punctate brain lesions were found within 3 days after a 2.57-Gy neutron exposure.[163] This effect was transient, and no degeneration was observed 30 days after irradiation. The lesions were not detectable using standard H and E stains. These effects are similar to a multi-infarction syndrome in which the effects of small infarctions accumulate and may become symptomatic. Since this pathology was observed at a dose of radiation previously believed to be completely safe, confirmation of these new data may profoundly influence our view of the radiosensitivity of brain tissue.

In an organ like the brain, different topographical regions may have varying susceptibility to ionizing radiation. The most sensitive area is the brain stem.[164] The brain cortex may be less sensitive than the subcortical structures,[157] such as the hypothalamus,[165] the optic chiasm, and the dorsal medulla.[166] Although radiation lesions tend to occur more frequently in brain white matter,[167-169] the radiosensitivity of white matter also appears to vary from region to region.[157]

In this regard, researchers have produced measures of the functional sensitivity of some brain areas and the insensitivity of others.[121,170] The activation of behaviors through electrical stimulation of the lateral hypothalamus (but not the septal nucleus or substantia nigra) is still possible after 100 Gy.[121,171] However, years after clinical irradiations, dysfunctions of the hypothalamus are prominent even without evidence of hypothalamic necrosis.[172] Local subcortical changes may exist in the reticular formation and account for radiation-induced convulsability of the brain.[173,174] Similarly, postirradiation spike discharges are more likely to be seen in the hippocampal electroencephalograph (EEG) than in the cortical EEG.[175] This idea of selective neurosensitivity is further supported by experiments in which electrical recordings were made from individual nerve fibers after irradiation.[176] These data reveal a hierarchy of radiosensitivity in which gamma nerve fibers are more sensitive than beta fibers, and alpha nerve fibers are the least sensitive.

The functional radiosensitivity of specific brain nuclei may in part explain the ability of a particular dose of ionizing radiation to disrupt one type of behavior but not another. For example, monkeys will continue to perform a visual- discrimination task but not a more physically demanding task (wheel running) after a similar dose of ionizing radiation.[59] These data agree with the suggestion that classically conditioned reflexes are more radioresistant than motor coordination, and that this selective disruption of particular behaviors “indicate[s] that ionizing radiation mainly affects the functions of the subcortico-[brain]stem formations of the brain.”[170]

The phenomenon of latent CNS radiation damage with doses above threshold has been well documented.[152,177,178] The long latent period has led to considerable speculation on the likely pathogenesis of late radiation lesions: *(a)* radiation may act primarily on the vascular system, with necrosis secondary to edema and ischemia, and *(b)* radiation may have a primary effect on cells of the neural parenchyma, with vascular lesions exerting a minor influence.[153]

The first evidence in support of a vascular hypothesis was obtained when human brains that had been exposed to X rays were examined.[154] It was suggested that delayed damage of capillary endothelial cells may occur, leading to a breakdown of the blood-brain barrier. This would result in vasogenic edema, the elevated pressure-impaired circulation of cerebral spinal fluid, and eventually neuronal and myelin degeneration.[159,179] The finding that hypertension accelerates the appearance of vascular lesions in the brain after irradiation with 10-30 Gy also supports a hypothesis of vascular pathogenesis.[180] The occlusive effects of radiation on arterial walls may cause a transient cerebral ischemia.[181] Sequential monkey-brain CAT scans revealed brain edema and hydrocephalis that accompanied hypoactivity and the animal's loss of alertness following 20 Gy of radiation.[182] The exposure of forty-five rabbit heads to 4, 6, or 8 Gy of X radiation produced a disturbance of the permeability of the blood-brain barrier that returned to normal only after 6 days.[183] The transient nature of the vascular phenomena may partially explain some of the behavioral deficits observed after exposure to intermediate or large doses of ionizing radiation.[184,185]

Evidence for the direct action of radiation on the parenchymal cells of the nervous system, rather than the indirect effect through the vascular bed, was first provided when brain tissue in irradiated human patients was examined.[186] None of the brain lesions could be attributed to vascular damage because they were *(a)* predominantly in white matter and not codistributed with blood vessels, *(b)* not morphologically typical of ischemic necrosis, and *(c)* often found in the absence of any vascular effects.[187-191] Thus, it appears that direct neuronal or glial mechanisms caused at least some of the observed radiogenic brain lesions.

In the brain, hypertension accelerates the onset of radiogenic vascular damage but not white matter lesions.[180] These data help to separate vascular damage from the pathogenesis of white-matter lesions, making it difficult to support the view that ischemia and edema are important in white-matter pathogenesis. It may be that selective necrosis of white matter is due to the slow reproductive loss of glial or their precursors. The radiosensitivity of certain types of glial cells (beta astrocyte) is well recognized.[192,193] The earliest sign of their damage is widening of the nodes of Ranvier and segmental demyelination as early as 2 weeks after a dose of 5-60 Gy.[194] Clinical evidence also suggests that radiogenic demyelination may occur. Several patients experienced sensations like electric shock (referenced to sensory levels below the neck) after radiotherapy for head and neck cancers.[195] The symptoms gradually abated and disappeared after 2-36 weeks. Similarly, this transient radiation myelopathy could be a result of temporary demyelination of sensory neurons. In addition, mitotic activity in the subependymal plate (important in glial production) did not recover after radiation doses producing necrosis, but did recover after doses not producing necrosis. This supports the hypothesis that glial are a primary target for radiogenic brain damage.[196]

Both vascular and glial changes may be important in the development of late radiation damage to the CNS.[153] The preponderance of one type of cell damage over another depends on the radiation dose used. “Vascular effects occur at lower dose levels but after a longer latent period than effects mediated through damage to the neuroglia.”[153] Perhaps the most important points for the present chapter are that *(a)* radiogenic brain damage is a well-accepted finding after high doses (greater than 15 Gy), and *(b)* it may occur after doses of less than 15 Gy under certain circumstances. The mechanisms of this damage are still debatable.

In addition to axonal demyelination, other direct neuronal damage may occur in the irradiated adult animal. Although mitotic neurons of the prenatal or neonatal CNS are known to be extremely sensitive to radiation, the neurons of more mature animals are thought to be quite resistant and less likely to result in cell death.[30,145,197] However, as early as 1962, neurogenesis was thought to take place in the cerebral cortex of adult rats.[198] Adult and juvenile neurogenesis was found to be especially prominent in the granule cell populations of the hippocampus and the olfactory bulb. These newly formed cells had the ultrastructural characteristics of neurons,[199] and the number of granule cells in the hippocampus increased in the adult rat.[200,201] Although these findings have not been confirmed in primates (thus reducing their ability to be generalized to the human), they suggest that certain neuron populations in the adult brain are radiosensitive due to their mitotic state.[202] Neurogenesis was reported in the hippocampal subgranular cell layer of the adult rabbit, and these cells were quite radiosensitive (4.0-4.5 Gy).[203,204]

Therefore, it may be that certain populations of proliferating neurons in the adult can be damaged or destroyed by relatively low doses of ionizing radiation.

Radiogenic changes in brain morphology are not limited to necrotic lesions or cell death. Subtle dendritic alterations following X irradiation, including decreased dendritic intersections, branchings, and length, as well as reduced packing density of neuronal elements in the irradiated cerebral cortex of the monkey, were reported.[205]

**Alterations in Nervous System Function**

Given the above data, we can say that (except for the possibility of mitotic neurons in the CNS) the adult brain is indeed relatively resistant to radiation when the end point measured is cell death or change in neuronal morphology. However, the point is that the CNS is quite sensitive to functional changes brought on by alterations in neurophysiology and neurochemistry. It is likely that these functional changes, brought about by low or intermediate doses (less than 15 Gy) of ionizing radiation, account for many of the behavioral changes observed.

Supporting this view, changes in brain metabolism were reported after very low (0.11-0.24 Gy) doses of ionizing radiation.[206] In a more detailed analysis with the $^{14}C$-2-deoxyglucose method of measuring local cerebral glucose utilization, a dose of 15 Gy of X radiation was administered to the rat brain.[207] Significantly lower rates of glucose use were found in sixteen different rat brain structures at 4 days after irradiation and in twenty-five structures at 4 weeks. Although large radiogenic changes exist in the metabolism of some brain nuclei, a weighted average rate for the irradiated brains, as a whole, was approximately 15% below that for the controls.

***Electrophysiology*.** Measures of electrophysiology have been used to illustrate changes in brain function after exposure to ionizing radiation. Several studies were reviewed in which cortical EEG changes were observed in humans and in animals following doses of less than 0.05 Gy.[208] Typically, an initial temporary increase in bioelectric amplitude was followed, within minutes, by a depression. Other investigations have frequently needed higher doses of radiation in order to observe changes in EEG. For example, changes were not seen in EEGs after 0.03-0.04 Gy, but significant alterations were observed after 2 Gy.[209] At a higher dose (15 Gy), monkey cortical EEG abnormalities consisted of the slowing of activity, with an increase in amplitude.[166] Spiking and patterns of grand mal seizure also occurred. A rapid onset of high-amplitude slow waves (delta waves) seemed to relate to periods of behavioral incapacitation.[210] Exposures to 4-6 Gy of gamma radiation seem to stimulate spontaneous activity in the neocortex, whereas exposures of higher than 9 Gy inhibit all brain activities.[211]

The hippocampus shows significant changes in physiological activities after gamma irradiation with even less than half of the 18-Gy threshold dose needed to produce changes in cortical activities.[164,212] One of the most striking effects was hippocampal spike discharges, first identified in cats[175] and later confirmed in rabbits.[212] This spiking developed soon after irradiation (2-4 Gy) when no other clinical signs of neurological damage or radiation sickness were present. The apparent radiosensitivity of the hippocampus and its importance in critical functions like learning, memory, and motor performance have recently led others to investigate the electrophysiology of this brain area. The firing of hippocampal neurons was found to be altered by exposure to 4 Gy of gamma radiation.[213] In addition, *in vitro* experiments suggest that spontaneous discharges of hippocampal pacemaker-like neurons are induced by X and gamma rays at a dose of 0.08 Gy.[214] If confirmed, these data suggest that hippocampal electrophysiology may be the most sensitive measure of functional brain changes after irradiation.

Alterations in the thresholds and patterns for audiogenic and electroconvulsive seizures have been produced by exposing animals to ionizing radiations. Such effects are generally interpreted as reflecting gross changes in CNS reactivity. Early work with dogs showed that spontaneous seizures sometimes occurred following very large doses of radiation.[154] Later experiments confirmed that seizures can be induced by whole-body or head-only exposures to 30-250 Gy in a variety of species. For example, rats were exposed to 5 Gy of X radiation and the electroconvulsive shock (ECS) threshold was determined for 180 days after irradiation.[173] ECS thresholds were reduced in irradiated rats over the entire test period. In later studies,[174] it was reported that considerably lower doses (perhaps less than 0.01 Gy) also reduced the thresholds for ECS seizures and audiogenic seizures.[215, 216]

Unlike the CNS, peripheral nerves are quite resistant to the functional alterations produced by ionizing radiation. Most data indicate that peripheral nerves do not show any changes in electrophysiology with X-ray exposures below 100 Gy.[217] After higher doses, the action-potential amplitude and the conduction velocity temporarily increase but then gradually decrease.[217-221] Also, alpha and beta particles are more destructive to peripheral nerves than are gamma or X rays, and usually cause a monophasic depression of function without the initial enhancement of activity.[222-224] Perhaps the lowest dose of ionizing radiation ever found to produce an alteration in the function of peripheral nerves was reported in a study in which T-shaped preparations of isolated frog sciatic nerves were produced when the nerves were partially divided longitudinally.[225] Electrical stimulation was applied to the intact stem of the T, and electrical recordings were made from the ends of the two branches. A small segment of one of the branches was irradiated with 0.04-0.06 Gy of alpha particles, producing a definite decrease in action-potential amplitude and an increase in chronaxie. These results are remarkable, given the much higher doses that have been required to affect these peripheral nerve functions in most other studies.

Relatively little radiobiology research has been done using single isolated nerve fibers. However, the results that do exist agree with those from experiments with nerve trunks. In single fibers isolated from a frog sciatic nerve, effects on peripheral nerve functions included the induction of an injury current in the irradiated segment and, with increased exposure, a sequence consisting of increased threshold, reduced action potential, and finally a conduction block.[224]

It has been known for some time that paralysis of the hind limbs of animals can result from localized irradiation of the spinal cord. Rabbits developed this paralysis at 4-33 weeks after exposure of the upper thoracic region to 30-110 Gy of X radiation at 2.5 Gy/day.[226] The minimum single exposure found to produce paralysis at 5 months was 20 Gy.[227] As in other model systems, the time interval between irradiation and the appearance of neurological symptoms decreases as dose increases. For example, 50 Gy of X rays to the monkey midthoracic spinal cord produced immediate paraplegia, whereas 40 Gy was effective only after a latent period of about 5.5 months.[228]

Radiation effects on the electrophysiology of the synapse were first studied using the cat spinal reflex.[229,233] These studies showed that excitatory synaptic transmission is significantly increased by X-ray exposures of 4-6 Gy. Synaptic transmission at the upper cervical ganglion of the cat is also facilitated 15-20 minutes after exposure to 8 Gy of X rays.[234] Both mono- and polysynaptic spinal reflexes are significantly augmented immediately after exposure to 5 Gy of X radiation. It is of interest that significant augmentation of monosynaptic excitatory postsynaptic potentials (EPSP) was found immediately after exposure to 6-12 Gy of X rays, whereas inhibitory postsynaptic potentials (IPSP) recorded from the same cell were not significantly affected by a 12-Gy exposure.[232,233] Similarly, polysynaptic EPSPs were significantly augmented as the dose increased, whereas the polysynaptic IPSPs were little influenced by even an exposure of 158 Gy. At higher doses (50-200 Gy), ionizing radiation may damage both synaptic and postsynaptic functioning, probably through different molecular mechanisms.[235] These radiogenic changes in synaptic transmission may be important factors underlying the complicated functional changes that occur in the CNS following radiation exposures.

***Neurochemistry.*** One of the most important mechanisms of postirradiation nervous transmission to be studied has been the ion flow across the neuronal semipermeable membrane. In particular, the flow of sodium ions is believed to be involved in the control of neuronal excitability[236] and apparently can be disrupted after either a very high or very low dose of radiation. A study using the radioactive isotope sodium-24 compared the sodium intake across the membrane of the squid giant axon before and after exposure to X rays.[237] A significant increase in sodium intake was found to occur during the initial hyperactive period induced by a dose of 500 Gy. These observations were confirmed in a study of frog sciatic nerves that had been irradiated with 1,500-2,000 Gy of alpha particles, although a simultaneous decrease in the rate of sodium extrusion also occurred[222] Peripheral nerves may be less radiosensitive than CNS neurons and perhaps differ in their radiation response. In a study that used a different technique, the artificially stimulated uptake of sodium into brain synaptosomes was significantly reduced by an ionizing radiation exposure (high-energy electrons) of 0.1-1,000.0 Gy.[238] This CNS effect was later confirmed for 1-100 Gy of gamma radiation.[239]

The brain has been described as a radiosensitive biochemical system,[206] and in fact, many significant changes in brain neurochemistry have been observed after irradiation. An early study revealed that 1-2 days after an exposure to 3 Gy of X radiation, neurosecretory granules in the hypophysial-hypothalamic system showed a transient increase in number over the controls.[240] A leaking of brain monoamines from the neuronal terminals of rats irradiated with 40 Gy of X rays has also been observed.[241] These changes in neuronal structure may correlate with radiogenic alterations of neurotransmitter systems.

Normal catecholamine functioning appears to be damaged following exposure to intermediate or high doses of ionizing radiation. After 100 Gy, a transient disruption in dopamine functioning (similar in some ways to dopamine-receptor blockade) was demonstrated.[242] This idea is further supported by the finding that a 30-Gy radiation exposure increases the ability of haloperidol (a dopamine-receptor-blocking drug) to produce cataleptic behavior.[243] Radiation-induced effects on dopamine have been correlated in time with ETI, suggesting that changes in this neurotransmitter system may play a role in behavioral disruptions. However, other neuromodulators (such as prostaglandins) also seem to influence dopaminergic systems to help produce some radiation-induced behavioral changes.[243] A transient reduction in the norepinephrine content of a monkey hypothalamus was also observed on the day of exposure to 6.6 Gy of gamma radiation. Levels of this neurotransmitter returned to normal 3 days later.[244] Similar effects have been reported,[245] but another study found no change in noradrenaline after 8.5 Gy of X rays.[246] Monoamine oxidase (MAO), an enzyme which breaks down catecholamines, was significantly reduced by a supralethal 200-Gy dose of mixed neutron-gamma radiation. This enzymatic change occurred within 4 minutes of exposure and lasted for at least 3 hours. In contrast, a very marked increase in MAO activity was observed when animals received the same dose of radiation rich in gamma rays.[247]

Contradiction exists in the literature concerning radiation's effects on 5-hydroxytryptamine (5-HT). Some investigators reported a radiogenic stimulation of 5-HT release at approximately 10 Gy, while others observed a decrease or no change in the levels of this neurotransmitter.[246] Although the physiological mediators of transient functional deficits may not be the mediators of radiation-induced mortality, it is interesting that dopamine and 5-HT have been suggested as radioprotectants for prolonging the survival of X-irradiated rats or mice.[248,249]

A variety of functions involving the neurotransmitter acetylcholine (ACH) is significantly altered by exposure to ionizing radiation. ACH synthesis rapidly increases in the hypothalamus of the rat after less than 0.02 Gy of beta radiation, but is inhibited at only slightly higher radiation doses.[206] A dose of 4 Gy of cobalt-60 gamma radiation produced a long-term increase in the rate of ACH synthesis in dogs.[250] Also, high-affinity choline uptake (a correlate of ACH turnover and release) slowly increased to 24% above control levels 15 minutes after irradiation with 100 Gy.[242] Choline uptake was back to normal by 30 minutes after exposure. Massive doses of gamma or X rays (up to 600 Gy) are required to alter brain acetylcholinesterase activity,[251] whereas much smaller doses depress plasma acetylcholinesterase by 30%.[252]

Cyclic nucleotides, such as cyclic AMP (adenosine-3',5'-cyclic monophosphate), act as second messengers in synaptic transmission. It is interesting that after irradiation (50 Gy), concentrations of cyclic AMP are reduced in rats[253] and monkeys.[254] The transient nature of these changes also suggests their possible role in EPDs.

Exposure to large doses of ionizing radiation results in postirradiation hypotension in monkeys,[111,255,256] with arterial blood pressure decreasing to less than 50% of normal.[257] Postirradiation hypotension also produces a decrease in cerebral blood flow immediately after a single dose of either 25 or 100 Gy of cobalt-60 gamma radiation.[127,258,259] This hypotension may be responsible for the ETI observed after a supralethal dose of ionizing radiation.[111,260,261] In support of this hypothesis, the antihistamine chlorpheniramine maleate was effective in reducing the monkeys' performance decrements and at the same time reducing postirradiation hypotension.[257] A study with untrained monkeys, whose postirradiation blood pressures were maintained by norepinephrine or other pressor drugs, showed that as long as arterial pressure remained above a critical level, the monkeys appeared to remain attentive and alert.[262] However, in a follow-up study on monkeys trained to perform a task, norepinephrine maintained blood pressure but did not consistently improve their performance during the first 30 minutes after irradiation.[263] Other authors have not seen a close association between blood pressure and behavioral changes.[210] Further contrary evidence was obtained from experiments with the spontaneously hypertensive rat (SHR), in which exposure to ionizing radiation reduced the blood pressure of most of them to near-normal levels. However, these irradiated SHRs still showed a significant behavioral deficit after exposure to 100 Gy of high-energy electrons.[264] Finally, a significant association was found between the degree of hypotension and the frequency of EPDs.[111] Still, half the monkeys with a 50% drop in blood pressure did not show behavioral decrements. Thus, even though the relationship between decreased blood pressure and impaired performance is intriguing, simple changes in blood pressure may not be sufficient to explain EPDs.

The massive release of histamine that is observed after exposure to a large dose of ionizing radiation has been proposed as a mediator of radiogenic hypotension and EPDs.[265] Histamine is a very active biogenic amine and putative neurotransmitter located in neurons and mast cells throughout the body, especially around blood vessels.[266] Attempts to alter the development of behavioral deficits by treating animals with antihistamines before exposure have been encouraging.[257,267] Monkeys pretreated with chlorpheniramine ($H_1$-receptor blocker) performed better and survived longer after irradiation than did controls.[267] Similar benefits were observed in irradiated rats.[268] Further, the use of diphenhydramine (a histamine $H_1$-receptor antagonist) inhibited radiation-induced cardiovascular dysfunction.[269] Since these antagonists produced only partial relief from radiation effects, it appears that the histamine hypothesis explains only a portion of the behavioral and physiological deficits observed after radiation exposure.[270]

When most animal species are exposed to a sufficiently large dose of ionizing radiation, they exhibit lethargy, hypokinesia, and deficits in performance.[30,54,121] Because these behaviors seem similar to those observed after a large dose of morphine, a role for endogenous opioids (endorphins) has been proposed in the production of radiation-induced behavioral changes.[271,272] Endogenous morphine-like substances may be released as a reaction to some[273-275] but not all[276] stressful situations. Like a sufficiently large injection of morphine itself, endogenous opioids can produce lethargy, somnolence, and reduction in behavioral responsiveness.[276,277]

Cross-tolerance between endorphins and morphine has been demonstrated for a variety of behavioral and physiological measures.[278,279] Given the similarity of ra diation- and opiate-induced symptoms, it is not surprising that endorphins appear to be involved in some aspects of radiogenic behavioral change. Ionizing radiation can produce dose-dependent analgesia in mice, and this radiogenic analgesia can be reversed by the opiate antagonist naloxone.[146] In another experiment, morphine-induced analgesia of the rat was significantly enhanced 24 hours after neutron (but not gamma) irradiation, suggesting some combined delayed effects of endogenous and exogenous analgesics that may be radiation-specific.[148] Ionizing radiation exposure can also attenuate the naloxone-precipitated abstinence syndrome in morphine-dependent rats.[280]

Further supporting the hypothesis that endorphins are involved in radiation-induced behavioral change, C57B1/6J mice exhibited a stereotypic locomotor hyperactivity similar to that observed after morphine injection, after receiving 10-15 Gy of cobalt-60 gamma radiation.[9] This radiogenic behavior was reversed by administering naloxone or by preexposing the mice to chronically stressful situations (a procedure that produces endorphin tolerance).[281] Further, opiate-experienced C57B1/6J mice reduced the self-administration of morphine after irradiation, suggesting that the internal production of an endorphin reduced the requirement for an exogenous opioid compound.[282] Biochemical assays also revealed changes in mouse brain beta-endorphin after exposure to ionizing radiation.[283] Rats and monkeys had enhanced blood levels of beta-endorphin after irradiation,[284,285] and morphine-tolerant rats showed less performance decrement after irradiation than nontolerant subjects.[286] In addition, naloxone (1 mg/kg) given immediately before exposure to 100 Gy of high-energy electrons significantly attenuated the ETI observed in rats.[284] Conversely, rats either underwent no change[62] or were made more sensitive to radiation effects after chronic treatment with naloxone on a schedule that increased the number of endorphin receptors.[287] However, the manipulation of opioid systems did not produce total control over postirradiation performance deficits. Thus, these data do not suggest an exclusive role for endorphins in radiogenic behavioral change.

## THE HUMAN EXPERIENCE WITH RADIATION

Humans have been exposed to radiation from environmental and industrial sources, clinical therapy, accidents, wartime detonations at Hiroshima and Nagasaki, and even experiments. Many of these exposures contribute little information about the behavioral effects of ionizing radiation. In most of the cases, behavioral data were not collected. Many of the data that were gathered are difficult to evaluate because there is no information about the radiation dose received, the level of baseline performance, or other circumstances. But the data are interesting, at least in a qualitative context, because they partially validate some work with animal models and also suggest new hypotheses for testing.

Two radiation accidents are particularly instructive. Both exposures occurred in the early days of the production of fissionable radiation material for nuclear weapons and involved radiation doses large enough to produce an ETI. In spite of safety precautions to ensure that the plutonium-rich holding tanks did not contain enough fissionable material to permit the occurrence of a critical reaction, an accidental critical event took place in 1958 at the Los Alamos Scientific Laboratory.[288] Mr. K. received an average (and fatal) total body dose of 45 Gy and an upper abdominal dose estimated at 120 Gy of mixed neutron-gamma radiation. During the event, Mr. K. either fell or was knocked to the floor. For a short period, he was apparently dazed and turned his plutonium-mixing apparatus off and on again. He was able to run to another room but soon became ataxic and disoriented. Because he kept repeating, “I'm burning up, I'm burning up,” his co-workers helped him to a shower, but by this time he could not stand unaided. He was incapacitated and drifted in and out of consciousness for over a half hour before he was rushed to a local hospital. Before his death at 35 hours after irradiation, Mr. K. regained consciousness and a degree of coherence. From approximately 2 to 30 hours after the accident, he showed significant behavioral recovery and at some points actually experienced euphoria, although his clinical signs were grave. The last few hours before Mr. K's death were characterized by irritability, uncooperativeness, mania, and eventually coma.[288]

The 1964 case of Mr. P., an employee of a uranium-235 recovery plant, closely parallels that of Mr. K. This accident took place in Providence, Rhode Island, when Mr. P. was trying to extract fissionable material from uranium scraps. A criticality occurred, and Mr. P. was thrown backward and stunned for a period of time. He received a head dose of 140 Gy and an average body dose of 120 Gy. Unlike Mr. K., however, Mr. P. did not lose consciousness. After a period of disorientation and confusion, he stood up and ran from the building to an emergency shack, a distance of over 200 yards. Mr. P.'s awareness of his surroundings during this early period has been questioned because he ran into a 4 inch-wide sapling even though it was quite visible. Unfortunately, Mr. P. rode in an ambulance for almost 2 hours, during which time behavioral observations were not made. When he arrived at Rhode Island Hospital, he had transient difficulty enunciating words. Significant behavioral recovery occurred from 8 to 10 hours after the accident. During this period, Mr. P. was alert, cooperative, and talked of future activities in a euphoric manner, inconsistent with his terminal diagnosis. In the hours before his death at 49 hours after the accident, Mr. P.'s condition deteriorated significantly, and he exhibited restlessness, anxiety, extreme fatigue, and disorientation.[289]

These cases of radiation accidents involving humans are consistent with the animal literature suggesting that a supralethal radiation dose can produce EPDs. Both of the accident victims experienced behavioral deficits to some degree soon after exposure. These deficits were transient and were most prominent in Mr. K. The data agree with general conclusions reached in a review of several radiation accidents, in which a remission of early symptoms occurred before the onset of the manifest illness phase was recorded.[290] In comparison with these high-dose accidents, lower radiation doses or partial-body exposures may produce milder but more persistent behavioral changes characterized by weakness and fatigability. An accident victim exposed to ionizing radiation from an unshielded klystron tube received as much as 10 Gy to portions of his upper torso and experienced fatigability that lasted for more than 210 days after exposure.[291]

The 1986 Chernobyl nuclear reactor accident also produced behavioral deficits in persons attempting to perform their duties in high-radiation environments. A Soviet fireman who fought the blaze of the burning reactor core suffered performance deficits and eventually had to withdraw because of his exposure to radiation.[292] Similarly, a Soviet physician who had received significant radiation exposures while treating patients could not perform his duties.[293] Both persons eventually recovered from their behaviorally depressed states and are (at this writing) still alive. These recent accident data add to the growing literature suggesting that sublethal doses of radiation can induce human performance decrements.

A few attempts have been made to assess human performance after clinical irradiations. The Halsted test battery for frontal-lobe functional deficits was used in four patients exposed to 0.12-1.90 Gy of mixed neutron-gamma radiations.[294] Test scores at days 1-4 and 1 year after exposure were within the normal range. Patients with advanced neoplastic disease were whole-body irradiated with 0.15-2.0 Gy given as a single dose or in 2-5 fractions separated by intervals of up to 1 hour.[42] The subjects were pretrained and served as their own controls in performing tests designed to assess hand-eye coordination. Tests were performed immediately after exposure and at later intervals, but at no time did a performance decrement exist that could be ascribed to these relatively low radiation doses. However, because the behavioral design of these experiments was secondary to medical treatment, the results are inconclusive. The paucity of radiobiological data on human behavior and the need to predict military performance after ionizing radiation exposure have led to an extensive Defense Nuclear Agency program on the estimation of human radiation effects.[295]

## RADIATION-INDUCED CHANGES IN MILITARY PERFORMANCE

The U.S. Army has predicted certain distributions of effect for combat personnel exposed to ionizing radiation. For every soldier who receives a radiation dose of greater than 30 Gy (a supralethal and behaviorally incapacitating dose), another will receive a lethal (4.5 Gy) dose that may alter behavior. Two more soldiers will receive doses that are sublethal but greater than the present maximum (0.5 Gy) allowed for troop safety.[296] Given this wide range of expected doses and the ambiguity of the expected outcomes for human behavior, the Defense Nuclear Agency established methods for estimating the behavioral effects of acute radiation doses (0.75-45.0 Gy) on combat troops.

To predict human radiation-induced performance deficits, the Defense Nuclear Agency used a survey method of first identifying the physical symptoms expected after various radiation doses and then determining the soldiers' estimates of their own changes in performance while experiencing these symptoms (Figure 7-8). Briefly, this involved *(a)* an extensive review of the literature on human radiation (including radiation-therapy patients, Japanese atomic-bomb victims, and radiation-accident victims) to identify the symptoms to be expected after the radiation doses of interest; *(b)* the compilation of symptom complexes that reflect various combinations of the expected radiogenic symptoms, including gastrointestinal distress, fatigability, weakness, hypotension, infection, bleeding, fever, fluid loss, and electrolyte imbalance;[297] *(c)* the development of accurate descriptions of the severity of each symptom category at each postirradiation time of interest; *(d)* an analysis of tasks performed by five different crews, including a field artillery gun (155-mm SP Howitzer) crew, a manual-operations field artillery fire-direction crew, a tank (M60A3) crew, a CH-47 (Chinook helicopter) crew, and an anti-tank guided missile crew in a TOW vehicle; *(e)* the development of questionnaires that require experienced crewmembers (NCOs or warrant officers) to predict task degradation (slowing of performance) during particular symptom complexes; and *(f)* the evaluation of monkey performance data from a visual-discrimination (physically undemanding) task or a wheel-running (physically demanding) task.[298] This analysis of animal data was performed, in the absence of sufficient human data, in order to estimate the rapid behavioral decrements that follow large (10-45 Gy) radiation doses.

For each crew position, sophisticated statistical techniques made possible the construction of minute-by-minute performance estimates and also smoothed the summary curves as a function of radiation dose and time (Figure 7-9). The analysis involved grouping the results from individual crew members into two categories: physically demanding tasks and physically undemanding tasks (Figures 7-10 and 7-11). A separate analysis of helicopter tasks was also made (Figure 7-12). The degree of performance deficit for each of the five crew positions was described in terms of the following categories: *(a)* performance capability 75%-100% of normal is *combat effective, (b)* performance capability 25%-75% of normal is *degraded,* and *(c)* performance capability 0-25% of normal is *combat ineffective.*

This scheme was then used to summarize the expected changes in the performance of combatants after various doses of radiation exposure.[295] In general, the data indicate that the capabilities of crew members performing tasks of similar demand are degraded similarly. The capabilities of crew members performing physically demanding tasks are degraded more than the capabilities of members performing physically undemanding tasks. This latter observation agrees with the data from animal studies on physical effort after irradiation (Figure 7-4). Figures 7-10, 7-11, and 7-12 illustrate the behavioral changes that might be expected during a one-month period after various doses of ionizing radiation. For example, if crew members performing a physically demanding task are exposed to 10 Gy (Figure 7-10), they will be combat effective for only a little over 1 hour. This period will be followed by an extended time (roughly 1 month) of degraded performance before they become combat ineffective before death. The outlook for performance (but not ultimate prognosis) is a little better for a person performing a physically undemanding task after a 10-Gy irradiation (Figure 7-11). This soldier would remain combat effective for 1.7 hours after exposure. Following this initial period of coping, a transient performance degradation of 2.8 days would ensue before a short recovery and then a gradual decline, ending in death at 1 month after irradiation.

In order to obtain an independent check of the performance degradations predicted for radiation sickness by this study, results were compared (where possible) to actual performance decrements measured in members of the U.S. Coast Guard. The decrements occurred during motion-sickness episodes with symptoms similar to those of radiation sickness. This comparison revealed that the estimates of radiogenic performance decrements made by responders to the questionnaire were similar to the actual declines in short-term task performance that were measured during motion sickness.

Although these are the best estimates of human radiation-induced behavioral deficits that are currently available, their limitations are recognized. These predictions apply to the physiological effects of prompt whole-body irradiation. The data do not predict the behavioral effects of protracted radiation exposures that would occur with fallout, nor do they attempt to account for degradation from the psychological effects that are unique to nuclear combat.

## RADIOPROTECTION AND BEHAVIOR

Relatively few studies have addressed the problem of normalizing the behavioral changes that are seen immediately (and up to 24 hours) after irradiation. Research suggests that antihistamines and opiate antagonists (such as naloxone) may offer behavioral radioprotection under certain circumstances. Some data suggest that estrogens (known to reduce lethal effects of ionizing radiation)[299,300] can reduce the intensity and duration of radiation-induced early transient behavioral deficits in castrated rats trained to perform an avoidance task.[56] Amphetamines can continue to produce locomotor hyperactivity in rats after irradiation with 100 Gy of electrons at a time when the animals would normally be hypoactive. Experiments have also been performed to evaluate the behavioral toxicity of radioprotectants that have the ability to *(a)* reduce the lethal effects of radiation or *(b)* challenge the emesis that sometimes accompanies intermediate doses of ionizing radiation.[62]

### Radioprotectants that Reduce Mortality

Traditionally, the development of radioprotectants has meant searching for compounds to protect from the lethal effects of ionizing radiation.[301] More recently, radioprotective compounds have been evaluated for their ability not only to decrease mortality but also to preserve behavioral capacities after irradiation.[62,302] Two early studies administered ndecylaminoethanethiosulfuric acid (WR-1607) (10 mg/kg, intravenous) to monkeys and reported some behavioral benefits.[90,303] In the first study, monkeys trained to perform a continuous-avoidance task were exposed to 100-400 Gy of pulsed neutron-gamma radiation.[90] Protection from ETI was observed up to 4 hours after irradiation, and WR-1607 extended the lives of the subjects for almost 5 hours beyond that observed in control animals. In the second study, monkeys trained to perform a visual-discrimination task were exposed to 25 or 40 Gy of mixed neutron-gamma radiation.[303] ETI was blocked during the first hour, but performance started to fall 2 hours after exposure. Although these behavioral results were promising, WR-1607 produced severe emesis. This side effect may explain the current shift of interest to another promising drug, WR-2721 (ethiofos).[302]

Many experiments have assessed the behavioral toxicity of drugs that are known to offer protection from radiation mortality. Researchers have been studying ethiofos extensively, hoping that it has fewer side effects than WR-1607.[301] Troops who are incapacitated on the battlefield from a radioprotectant are as great a loss as troops incapacitated by ionizing radiation. Ethiofos has been tested in mice, rats, and monkeys for its behavioral toxicity and its potential ability to block radiogenic performance decrements, using spontaneous locomotor activities as well as accelerating-rod and visual-discrimination performance tests.[62,75,98,101,302,304-306] In all of the species and tasks analyzed, ethiofos was behaviorally toxic when given alone (it disrupted trained behavior or it reduced locomotor activity), and it increased rather than decreased the radiation-induced performance decreements. Thus, although ethiofos protects from the lethal effects of radiation, it has limited use when the recipient must remain functional. This concept of a behaviorally tolerated drug dose is very important in evaluating the radioprotectant candidates for military use.

**Efficacy of Antiemetics**

Although considerable research on antiemetics exists, its focus has been mainly limited to drugs that are effective in radiation therapy.[96,307,308] In this regard, various anti-inflammatory drugs (such as dexamethasone and steroids) have been useful in managing the emesis of patients.[309, 310] However, therapy makes few task demands on the recipients; in the military, antiemetics that are effective against radiation-induced vomiting must also not disrupt performance capabilities. These requirements significantly reduce the field of potentially useful antiemetics. For example, metoclopramide, dazopride, and zacopride (5-HT3-receptor blockers) were tested for antiemetic effects in monkeys exposed to 8 Gy of gamma radiation.[308] All three drugs were found to be effective antiemetics. However, only zacopride had no readily observable behavioral effects; metoclopramide disrupted motor performance, and dazopride produced drowsiness.[95] Additional work assessed the behavioral toxicity of zacopride in monkeys performing the speed-stress visual-discrimination task[311] and in rats performing the accelerating-rod task.[312] No behavioral toxicity was observed in either performance model. In the future, these more refined behavioral measures will be used to assess the military usefulness of these and other putative antiemetics after radiation exposure.

**Shielding**

In addition to pharmacological radioprotection, the immediate effects of radiation may be mitigated by shielding (placing material between the radiation source and the subject). Studies have focused on either head shielding (body exposed) or body shielding (head exposed). In one study of ETI, pigs were trained to traverse a shuttle-box on cue and then were either body-exposed or head-exposed to 60-130 Gy of mixed neutron-gamma radiation.[313] The investigators reported that head shielding offered significant protection from ETI. Other short-term shielding experiments were conducted with monkeys trained to perform a visual-discrimination task.[118,314] The monkeys were exposed to mixed neutron-gamma radiation at doses of 25, 45, or 100 Gy. In the 25- and 100-Gy-dose groups, ETI was about equally severe for all shielding conditions. However, the incidence of ETI in the 45-Gy-dose group was lowest in the head-shielded condition. The results from several other shielding studies with monkeys do not clearly indicate that head or body shielding offers any differing protection from ETI.[127,258,260,315,316] These equivocal results also raise questions about the exclusive role of the CNS in the production of radiation-induced performance deficits. As with radiation-induced taste aversion, postirradiation behaviors may be influenced by peripheral mechanisms that have not been fully explored.[94]

### Bone-Marrow Factors

Bone-marrow transplants have been used to challenge radiation-induced damage to the blood-forming systems. It is interesting that this manipulation seems also to provide some subchronic behavioral benefits.[317] Measures of activity and lethality were recorded in rats that were irradiated with 6.5 Gy of X rays. Twenty percent of the nontreated rats died, whereas 86% of the marrow-treated group survived. It is more important here that the initial decreases in spontaneous locomotor activity were less severe in the marrow-treated rats. Instead of showing a second drop in activity 10 days after irradiation, the treated rats showed near-normal activity for the entire 35 days of testing.[71] A similar outcome for behavior was observed in rats exposed to 7.5 Gy of whole-body X rays except for shielded marrow-containing bones.[317]

Bone-marrow transplantation may be impractical in military situations. However, shielding may enable stem cells to survive so that certain immunomodulators of growth factors may promote regeneration and thereby enhance performance.

### Radiation in Space

The behavioral scientist who is interested in these issues is constantly challenged by a variety of military-relevant tasks that require empirical analysis. As military operations move to outer space, new radiation hazards will challenge the human's abilities to carry out missions.[86,318] The behavioral effects of ionizing radiations (such as protons and high-Z particles) in space are beginning to be explored.[319,320] Preliminary indications are that radiations in space may be significantly more disruptive to behavior than are the radiations in the earth's environments.

## SUMMARY

The success or failure of military operations can be measured in terms of missions completed or tasks performed. Under many circumstances, exposure to ionizing radiation can significantly impede performance. In the case of low-to-intermediate doses of radiation (up to 10 Gy), performance deficits may be slow to develop, may be relatively long lasting, and will usually abate before the onset of chronic radiation effects, such as cancers. After large doses, the behavioral effects are often rapid (within minutes), and they usually abate before the onset of the debilitating chronic radiation sickness. These rapid effects can also occur after intermediate doses. But all tasks are not equally radiosensitive; tasks with complex, demanding requirements are more easily disrupted than simple tasks. The exceptions may be certain naturalistic behaviors which are also quite radiosensitive. Radiation parameters such as dose, dose rate, fractionation, and quality can all influence the observed degree of performance decrements. Electron radiation is more able to produce behavioral deficits than are other radiations, such as neutron radiation. In addition, combined injuries will probably be prevalent in any future nuclear conflicts; present data suggest that trauma can act synergistically with radiation exposure to greatly increase the behavioral deficits.

Possible sensory and neurophysiological mediators of radiation-induced behavioral deficits have been identified. Long-term changes in performance may be mediated in part by radiogenic brain damage from ischemia, edema, or direct damage to the parenchymal tissues themselves (such as dendrites and glial). More transient cerebrovascular changes after radiation exposure may also produce short-lived behavioral deficits. Postirradiation alterations in brain metabolism and the disruption of the normal electrophysiology of the axon and synapse may have important roles in certain performance deficits. In addition, a wide range of radiogenic neurochemical alterations have been characterized. These include the reduced ability of synaptic sodium channels to respond to stimulation. The nervous system's radiosensitivity is revealed by the fact that alterations in the basic substrate of neural excitation have been observed at doses of less than 1 Gy. Various levels of neurotransmitters (such as acetylcholine and dopamine), putative neurotransmitters (such as endorphins), and other neurochemicals and biogenic amines (such as histamine) undergo significant changes after radiation exposure. Like the modifications of morphology and electrophysiology, many of these neurochemical changes may also be capable of mediating the performance decrements observed after ionizing radiation exposure.

The literature on performance deficits in animals is quite extensive compared to that for humans. Human data are derived from radiation accidents or therapeutic studies, and many confirm the information from animal studies. Based on all data now available, the Human Response Program of the Defense Nuclear Agency has estimated the expected performance changes in irradiated soldiers. These projections depend on such factors as radiation dose, time after exposure, and task difficulty. Although the topics are complex, the human and laboratory animal data should permit the description, prediction, and (eventually) amelioration of the behavioral effects of ionizing radiation exposure. Thus far, however, many of the pharmacological compounds that protect animals from the lethality of ionizing radiation have been found to have severe behavioral toxicity. We must further explore the potential for using behaviorally compatible antiemetics and selective physical shielding to help maintain performance after radiation exposure.

## REFERENCES

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